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Review

Telomeres in a spatial context: a tool for understanding ageing pattern variation in wild populations

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Ageing refers to the loss of organismal functionality with age, a process that is characterised by decreased reproduction and survival probability. In natural populations, it is expected that environmental conditions influence an individual's ageing trajectory. Understanding the role of environmental heterogeneity on ageing variation could provide critical insights into population resilience and species distribution but remains overlooked. Telomeres, the end cap of chromosomes, are a promising integrative physiological marker of an individual's health and a possible proxy to aid the understanding of variation in ageing trajectories. Here, we review the existing information on telomere length and its dynamics in wild populations distributed across spatial scales. Despite a relative scarcity of information, there is evidence for divergence in telomere length between populations facing contrasting environments. Nonetheless, a higher spatial resolution and temporal replication are needed to fully understand the role that environmental conditions play on telomere length variation. Since most of the existing studies are correlational, future field and laboratory experiments are required. For the first time, we demonstrate the use of population telomere data to predict species habitat suitability through species distribution models (SDMs). This represents a promising new research area in the study of ageing pattern variation in wild populations. Furthermore, the inclusion of telomere data in future physiological SDMs may improve our understanding of species distribution and population resilience. However, the use of telomeres within this context could be limited if no previous knowledge on the relevance of telomeres as markers of health and survival at the species level is available. Finally, we suggest some key practical and theoretical considerations that, ideally, future studies combining biogeographic and telomere data should pay attention.

Keywords: biogeography, macrophysiology, senescence, spatial patterns, species distribution models, telomere length

Introduction

Ageing is a widespread phenomenon across the tree of life defined by a decline in organismal functionality and a decrease in reproduction and survival probability with time (Williams 1957, Jones et al. 2014). However, natural populations are exposed to

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dynamic environmental conditions, and only recently we have begun to understand how shifts in these conditions can modulate the pace of ageing either at the individual or populational level (Gaillard and Lemaître 2020). Harsh conditions are known to accelerate ageing by unbalancing the maintenance of health over a lifespan (Acevedo-Whitehouse and Duffus 2009). Likewise, benign conditions can enhance fitness and survival, as observed in species with a faster pace of life under captive conditions (Tidière et al. 2016). In addition, events over an individual's lifespan, such as reproduction or migration, are known to alter ageing patterns (Nussey et al. 2007, Bouwhuis et al. 2010, Cooper and Kruuk 2018). Recently, the study of molecular mechanisms, such as immunological and oxidative stress parameters, has provided important insights into the mechanistic causes behind the age-related increase in mortality within and across wildlife populations (Monaghan et al. 2009, Selman et al. 2012, Peters et al. 2019). In this line, the shortening of telomeres (the end cap of chromosomes), is generally considered an indicator of health and ageing in biomedical and epidemiological research (Aubert and Lansdorp 2008, Muñoz-Lorente et al. 2019), which explains the increasing interest for telomeres in eco-evolutionary studies (Monaghan et al. 2018). In wildlife, the study of telomeres across populations may provide insights into how organisms cope with environmental variation and improve our understanding of species distribution and resilience (Fig. 1). Furthermore, this knowledge could also improve predictions of future broad-scale patterns through the projection of biophysical and mechanistic models into geographical space (i.e. species distribution models, SDMs; Fig. 1; Talluto et al. 2016, Becker et al. 2020, Rubalcaba and Olalla-Tárraga 2020).

In this review and synthesis, we not only aim to summarise the available information on telomeres across spatial patterns, but also to promote a novel approach of combining biogeographic tools and telomere length information. First, we provide an overview of key environmental factors or drivers that are known to generate variation in telomere length (Fig. 1). Next, we present a systematic review of the available studies estimating telomere length within a spatial context. We exemplify the possible outcomes of combining, through SDMs, environmental predictors with telomere data. Finally, we discuss some theoretical and practical considerations that, ideally, studies estimating telomere length across spatial patterns should take into consideration.

The use of telomeres in eco-evolutionary studies

From a molecular perspective, telomeres are nucleoprotein structures comprised of non-coding tandem repeats of base pairs (TTAGGG and TTAGG in most vertebrates and arthropods studied to date, respectively; Fig. 1a), localised at the end of the eukaryotic chromosomes (Blackburn 1991, 2005). In somatic cells, telomeres shorten after each cell division in the absence of the expression of restoration mechanisms such as the enzyme telomerase (Blackburn 2005; Fig. 1b). The activity of telomerase is often downregulated after birth, which likely explains the negative relationship between telomere length and age observed across taxa (Olsson et al. 2011, Heidinger et al. 2012, Louzon et al. 2020, Sánchez-Montes et al. 2020, Froy et al. 2021), although this pattern might not be universal (Hoelzl et al. 2016, Ujvari et al. 2017). As discussed below, the rate of telomere shortening is often increased under energy-demanding processes that involve allocation of resources from telomere maintenance to other functions. Among these functions, environmentally induced oxidative stress is suggested as one of the drivers of faster telomere erosion (von Zglinicki 2002, Reichert and Stier 2017, Chatelain et al. 2020). At the organismal level, studies on laboratory models and humans have shown that shorter telomeres trigger age-related pathologies and shorten lifespans (Blasco 2005, Muñoz-Lorente et al. 2019). In wild populations, shorter telomeres are generally associated with increased mortality risk, although current knowledge is mostly restricted to birds and mammals, and the relationship has been shown to be context-dependent in some cases (McLennan et al. 2017, Wilbourn et al. 2018). Also, telomere length can help to predict important life-history traits such as lifespan (in birds: Heidinger et al. 2012, Bichet et al. 2020, in mammals: van Lieshout et al. 2019), lifetime reproductive success (in birds: Eastwood et al. 2019) or individual quality (foraging behaviour, body size or hatching success; in birds: Angelier et al. 2019; in reptiles: Rollings et al. 2017; in amphibians: Cheron et al. 2021). However, despite that some studies highlight the relevance of telomeres as markers of survival and health status, further research is needed as their predictive value has not been explored broadly across taxa and species-specific differences might exist (Wilbourn et al. 2018, Chatelain et al. 2020).

It is important to note that studies based on both laboratory and natural populations indicate that a significant proportion of an individual's telomere length can be explained by environmental variation, i.e. harsher or unpredictable environments are linked to shorter telomeres or faster telomere shortening rate (Watson et al. 2015, McLennan et al. 2016, Angelier et al. 2018, Seeker et al. 2021; meta-analysed in Chatelain et al. 2020). Telomeres seem to be particularly sensitive to environmental variation at early life stages, including prior to birth or hatching (Haussmann et al. 2012, Noguera et al. 2020, Stier et al. 2020) or via maternal effects and parental life histories (Haussmann et al. 2012, McLennan et al. 2018). These pre-natal or early postnatal effects on offspring telomeres may have consequences not only on an individual's telomere dynamics but also on the ageing patterns in subsequent generations (Haussmann and Heidinger 2015; Fig. 1). Indeed, in wildlife populations, it has been shown that the environmental conditions experienced during early life can generate long-lasting cohort effects on telomere length (Spurgin et al. 2018, van Lieshout et al. 2019). Likewise, the influence of previous variation in the abiotic and biotic components can have a bigger impact on telomeres than the current ones (Debes et al. 2016); therefore, this is another relevant aspect to consider when investigating telomere dynamics in wildlife inhabiting contrasting environments.

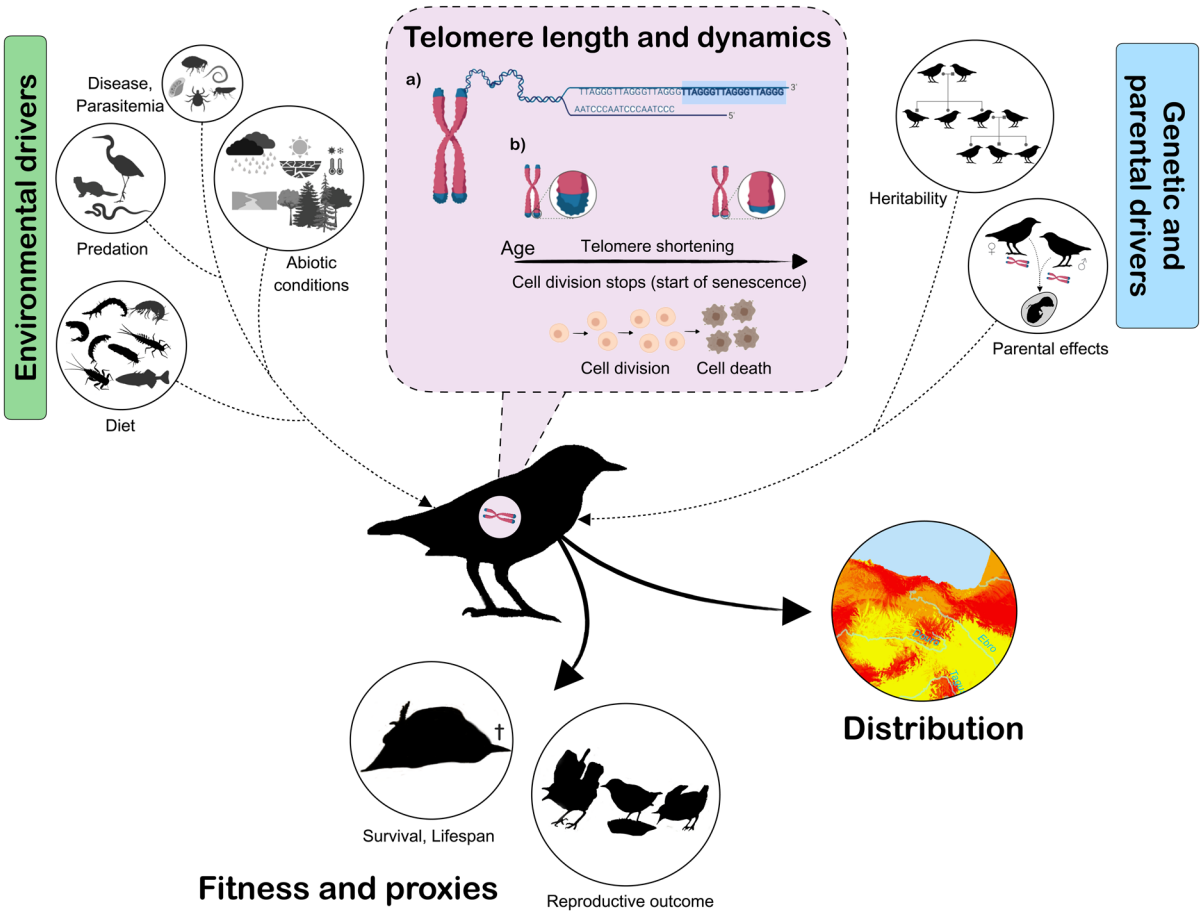

Figure 1. Diagram on the possible link between telomere length, species distribution and ageing pattern across spatial scales. Telomeres are dynamic molecular structures acknowledged to integrate physiological responses to environmental conditions and individuals' health. Therefore, the measurement of telomere length arises as a promising tool to evaluate population status and understand species resilience and distribution. Telomere length variation among individuals is explained by environmental drivers (green) and genetic and parental drivers (blue). The biogeographical differences in these drivers across the landscape may contribute to the variation in telomere length and its dynamics among individuals, influencing organisms' fitness and ultimately species distribution. (a) Representation of a chromosome highlighting the structure of vertebrate telomeric motif. (b) Telomeres get shorten in each cell replication as the result of the normal cell division process, yet the rate of shortening can differ among individuals due to life-history events and environmental conditions experienced over a lifetime. Figure created with BioRender.com.

The evolutionary relevance of the relationship between fitness-related traits, environmental conditions and telomere dynamics should be discussed considering the heritability component of telomere length. Although telomere length is often considered to be a heritable trait, heritability estimates are highly variable across taxa as they range from 0.06 to ~1 (Haussmann and Heidinger 2015, Reichert et al. 2015, Dugdale and Richardson 2018, Bauch et al. 2021, Boonekamp et al. 2021, Sparks et al. 2021, van Lieshout et al. 2021, Vedder et al. 2021). Also, although the evolvability of telomeres has not yet been fully explored, it seems to be low in some taxa (Bauch et al. 2021, Sparks et al. 2021, van Lieshout et al. 2021; but see Froy et al. 2021), and the environmental effects detected in some studies are surprisingly small (Bauch et al. 2021, Vedder et al. 2021). Some strong genetic correlations between telomere length and lifespan have been recently described in bird and mammal species (Froy et al. 2021, Vedder et al. 2021), which may imply that telomere length can act as a biomarker of lifespan set at conception. Nonetheless, we still lack a complete picture of the relative contribution of genetic and environmental components to telomere dynamics, nor its evolvability, which makes it difficult to fully understand the transgenerational effects of environmental variation on wildlife telomeres, and therefore, more studies are needed in this direction.

Environmental drivers of telomere length variation

Energetic resources are finite in natural populations, and precisely how individuals allocate these resources to different traits will have implications for their performance and fitness. For example, growth at early developmental stages is

often an energy-demanding process, possibly explaining that harsh environmental conditions during early life frequently involve carry-over effects for development, ageing pattern and reproductive senescence at adult stages (Nussey et al. 2007, Cooper and Kruuk 2018). Detrimental conditions over the lifespan can drive age-specific changes in physiological pathways linked to fitness, such as those mechanisms involved in the resistance to parasites or in the oxidative stress response (Boots 2011, Pamplona and Costantini 2011), and ultimately, shape the relationship between these physiological markers and important life-history traits such as lifespan (Marasco et al. 2017). Empirical studies are increasingly showing the existence of links between telomere dynamics and the exposure to environmental conditions (Fig. 1), both at early and adult stages. For example, changes in telomere length have been observed in relation to variation in abiotic or biotic conditions, such as the hydric regime (Dupoué et al. 2020), temperature (Simide et al. 2016, Nowack et al. 2019, Burraco et al. 2020a), predation risk (Kärkkäinen et al. 2019), nutrient quality (Noguera et al. 2015) or exposure to parasites (Asghar et al. 2015). Anthropogenic disturbances such as the ones linked to urbanisation (Ibáñez-Álamo et al. 2018) or pollution (Matzenbacher et al. 2019) have also been associated with shorter telomere lengths. Theoretically, under stressful conditions, faster telomere shortening could be the consequence of the prioritisation of processes ensuring immediate survival rather than telomere maintenance (Casagrande and Hau 2019), a pattern that may be exacerbated at early life stages (Monaghan and Ozanne 2018, Young et al. 2018). However, the relationship between environmental conditions and telomeres still deserves further exploration, as several studies have reported no effect of detrimental conditions on telomeres, even under poor conditions such as light pollution or chemical toxicants (Sletten et al. 2016, Blévin et al. 2017, Ouyang et al. 2017). These differences between studies highlight that telomere dynamics in response to environmental shifts can be complex, denoted by marked developmental-stage or sex-dependent relationships between telomere length and environmental conditions (Yip et al. 2017, Dorado-Correa et al. 2018).

Nonetheless, despite the study of the pathways involved in telomere dynamics under environmental change still needs further exploration, it could also greatly improve our understanding of the significance of an individual's telomere length at a given time point. For example, some studies suggest that the expression of the ribonucleoprotein telomerase (responsible for replication of telomeric regions) can be upregulated in response to stressful environments, which contrary to expectations, may lead to longer telomere lengths in less benign environments (Beery et al. 2012, Kesäniemi et al. 2019). However, it is still unknown whether environmentally driven alterations of telomerase expression may directly influence fitness or lifespan and thus have long-term implications at the individual level. Independently from the telomere maintenance mechanisms, detrimental conditions have been suggested to induce antioxidant responses to reduce the putative damage caused by free radicals derived from elevated catabolism, which may buffer telomere shortening (Chatelain et al. 2020). However, this commonly suggested link between high metabolism and telomere shortening must be carefully considered as the regulation of mechanisms such as mitochondrial uncoupling can also reduce the production of reactive oxygen species (ROS) under elevated energetic demand, thus preventing oxidative stress and the likely damage on telomeres (Stier et al. 2014, Hou et al. 2021). Despite its complexity, the study of the mechanisms involved in the repair, maintenance or buffering of telomere shortening represents a promising research avenue that will help to better understand between-population variation in telomere dynamics.

Telomere dynamics across spatial scales

While the study of telomeres is well established at the organismal level, at least for some species, the implications that different environmental conditions have on telomere variation across broad spatial patterns are still an overlooked aspect in eco-evolutionary studies. According to the current knowledge on telomere biology, it is possible that the information on individual telomere length across populations could be used as a surrogate to understand species resilience to environmental change (i.e. conservation physiology: Cooke et al. 2013, Chown and Gaston 2016). To synthesise the current information on environmental conditions and telomere length in spatially distributed wild populations, we conducted a systematic search in PubMed in March 2021 using the following search string: ('telomere') AND (environment* OR geograph* OR latitud* OR landscape* OR habitat* OR populations OR range* OR biotic* OR abiotic* OR anthropogo*) NOT (human* OR domestic* OR captiv* OR plant* OR aquacultur*). We screened titles, abstracts and finally full texts, and we included those studies that estimated telomere length in wildlife from a spatial perspective (Supporting information). Finally, we considered that 34 studies met the requirements to be included in this review (Table 1, Supporting information). Despite a relative scarcity of studies quantifying telomeres within a spatial context, the available literature already evidences the existence of divergence in telomere length and/or its dynamics in populations exposed to contrasting environments (Table 1). This provides a promising initial step for the use and implementation of this molecular marker to advance our understanding of ageing patterns across populations and the role of environmental heterogeneity shaping it. However, further effort is needed, especially in those taxa and species where the use of telomeres as health or fitness biomarker have not been validated yet, a pre-requisite for considering telomeres informative in spatial studies and for their implementation in mechanistic models.

Studies on endotherms

A considerable number of studies have explored the variation in telomere length and its dynamics in bird populations under different environmental regimes. While most of the

Table 1. Overview of studies assessing telomere length and/or its dynamics across spatial patterns. TL = telomere length; TL method = laboratory method for the telomere estimates; TL or dynamics: whether telomere length was measured once (length) or multiple times (dynamics) per individual.

Species	Spatial context	Environmental variation	TL or dynamics	TL method	Association between telomeres and the spatial context	Reference
Bird *Acrocephalus sechellensis*	1 population; 110 territories	Territory quality	Dynamics	qPCR	Faster TL shortening in males living next to unfamiliar male neighbours	Bebbington et al. 2017
Bird *A. sechellensis*	1 population; 22 cohorts	Territory quality	Dynamics	qPCR	Positive relation between TL and insect abundance	Spurgin et al. 2018
Bird *Aphrastura spinicauda*	2 populations	Latitudinal variation	Length	qPCR	Trend of shorter TL at low latitude	Quirici et al. 2016
Bird *Ficedula hypoleuca*	1 population; 2 habitats	Habitat quality	Dynamics	qPCR	Shorter TL in females breeding in high predator density; faster TL shortening in nestlings in control habitat (cross-fostering)	Kärkkäinen et al. 2019
Bird *F. hypoleuca*	6 populations	Spatial distribution	Dynamics	qPCR	Between-population variation in TL (developmental stage and growth dependent) and in paternal TL heritability	Kärkkäinen et al. 2021
Bird *F. hypoleuca*	1 population; 2 habitats	Habitat pollution	Length	qPCR	No difference in nestling or adult TL between habitats	Stauffer et al. 2017
Bird *Parus major*	4 locations, nest boxes at varying distances from roads	Urbanisation	Dynamics	qPCR	Faster TL shortening in nestlings closer to roads, no effect of metal exposure	Grunst et al. 2020
Bird *P. major*	2 populations; 2 habitats (urban/rural)	Urbanisation	Length	qPCR	Shorter TL in the urban habitat (cross-fostering)	Salmón et al. 2016
Bird *P. major*	2 populations; 2 habitats (urban/rural)	Urbanisation	Dynamics	qPCR	No difference in TL shortening between habitats	Salmón et al. 2017
Bird *P. major*	1 population; 2 habitats	Habitat pollution	Length	qPCR	Shorter TL in nestlings in the polluted habitat; no difference in adults	Stauffer et al. 2017
Bird *P. major*	3 populations	Elevation	Dynamics	qPCR	Faster telomere shortening with elevation	Stier et al. 2016
Bird *P. major*	2 populations; 2 habitats (urban/rural)	Urbanisation	Length	qPCR	No difference in TL between rural and urban 14-days old chicks	Biard et al. 2017
Bird *Periparus ater*	2 populations	Elevation	Dynamics	qPCR	Faster telomere shortening with elevation	Stier et al. 2016
Bird *Saxicola torquatus axillaris* and *S. rubicola*	7 populations; 2 species/latitudes	Latitudinal variation	Length	TRF-Southern blot	Shorter TL in first year pre-breeding individuals of *S. rubicola* (temperate environment) than in *S. torquatus axillaris* (tropical environment)	Apfelbeck et al. 2019
Bird *Setophaga ruticilla*	1 population; 2 habitats	Habitat quality	Dynamics	qPCR	Faster TL shortening in low-quality wintering habitat	Angelier et al. 2013
Bird *Tachycineta bicolor*	1 population; 2 habitats	Habitat pollution	Dynamics	TRF-Southern blot	Faster TL shortening with traffic noise	Injaian et al. 2019
Bird *Turdus merula*	10 populations; 2 habitats (urban/rural)	Urbanisation	Length	TRF-in-gel	Shorter TL in urban habitats	Ibáñez-Álamo et al. 2018
Bird *Uria lomvia*	3 populations	Spatial distribution	Length	TRF-Southern blot	Shorter TL in birds from low-quality colony	Young et al. 2013
Bird *U. lomvia*	4 populations	Spatial distribution	Dynamics	TRF-Southern blot	Sex-dependent difference in TL shortening between colonies (productivity)	Young et al. 2015

Continued

Table 1. Continued.

Species	Spatial context	Environmental variation	TL or dynamics	TL method	Association between telomeres and the spatial context	Reference
Mammal *Myodes glareolus*	2 populations	Habitat pollution	Length	qPCR	Shorter TL in a more polluted habitat (radiation, Chernobyl)	Kesäniemi et al. 2019
Mammal *Capreolus capreolus*	2 populations; 2 habitats	Habitat quality	Length	qPCR	Shorter TL in poor environment (only in older individuals)	Wilbourn et al. 2017
Mammal *Ctenomys torquatus*	3 populations	Habitat pollution	Length	qPCR (absolute TL)	Shorter TL in more polluted habitats with coal	Matzenbacher et al. 2019
Mammal *Ursus americanus*	1 metapopulation	Latitudinal variation	Length	qPCR	Shorter TL at higher latitude	Kirby et al. 2017
Fish *Salmo salar*	1 population; 2 habitats	Habitat characteristics	Length	qPCR	Faster TL shortening in a harsher habitat	McLennan et al. 2016
Fish *S. trutta*	10 populations (rivers)	Habitat characteristics	Length	qPCR	Shorter TL in rivers with warmer temperature	Debes et al. 2016
Fish *Squalius cephalus*	2 environments; 4 sites (urban), 2 sites (agriculture)	Urbanisation and habitat pollution	Length	qPCR	Shorter telomeres in fish from urban and with high pollutant rivers	Molbert et al. 2021
Reptile *Caretta caretta*	2 habitats, 1 site per habitat	Feeding habitat use	Length	qPCR	No difference between habitats	Hatase et al. 2010
Reptile *Niveoscincus ocellatus*	2 populations; 2 habitats	Elevation	Dynamics	qPCR	TL shortening did not differ between altitudes	Fitzpatrick et al. 2019
Reptile *Psammodromus algirus*	6 populations	Elevation	Length	qPCR	TL differs among populations but independent of altitude	Burraco et al. 2020b
Reptile *Zootoca vivipara*	10 populations	Habitat quality	Length	TRF-Southern blot	Shorter TL in populations with higher extinction risk	Dupoué et al. 2017
Amphibian *Epidalea calamita*	6 populations; 3 habitats	Variation in body size across latitude	Length	qPCR	TL differs between populations but independently of habitat characteristics	Hyeun-Ji et al. 2020
Amphibian *Hyla sarda*	2 populations, 7 sites	Biogeographic history	Dynamics	qPCR	No TL change within historically stable populations, elongation within a population arisen during a recent expansion	Canestrelli et al. 2021
Amphibian *Rana temporaria*	1 population; 3 habitats	Habitat characteristics	Length	qPCR	Shorter TL in habitats with higher historical desiccation risk	Burraco et al. 2017
Bivalvia *Arctica islandica*	2 populations	Spatial distribution	Length	TRF-Southern blot	No TL differences between populations	Gruber et al. 2014
Asteroidea *Coscinasterias tenuispina*	4 populations; 2 oceanic basins	Spatial distribution	Length	qPCR	Longer TL in Mediterranean populations than in Atlantic populations	García-Cisneros et al. 2015
Equinoidea *Paracentrotus lividus*	3 populations	Habitat pollution	Length	qPCR	No change in TL between populations, but the relationship between TL and body size was significant only in populations contaminated with trace elements	Coupé et al. 2019

research has focused on a narrow spatial scale, a couple of studies stand out comparing telomere length between biomes and contrasting latitudes. The first study compares age-related telomere length in two phylogenetically closed stonechat species inhabiting contrasting environments (i.e. tropical and temperate, Apfelbeck et al. 2019). Tropical African populations of *Saxicola torquatus axillaris* live in a more benign environment with lower extrinsic mortality than temperate populations of *Saxicola rubicola*. Stonechats from both regions showed similar telomere length as nestlings; however, pre-breeding, first-year individuals had longer and shorter telomeres in tropical and temperate regions, respectively. Later, during the first breeding season, this cross-sectional approach shows that telomere length returned to be similar between species. Another study on a South American songbird with a wide distribution range, the thorn-tailed rayadito *Aphrastura spinicauda*, compares the telomere length of two populations at the latitudinal extremes of the species geographic distribution (Quirici et al. 2016). At low latitude, this species shows lower brood size, nestling body mass, primary productivity and interestingly, nestlings have higher levels of corticosterone (the main stress-related hormone in birds) and shorter telomere length (Quirici et al. 2016). Moreover, other studies have also made use of spatially distributed populations but at a similar latitude. For instance, in Brünich's guillemots *Uria lomvia*, a seabird species, differences in telomere shortening are linked to breeding colony, from the Aleutians to Svalbard, which suggests that the environmental quality in each colony is the main driver of adult telomere length (Young et al. 2013). This study also highlights the role that gradients of natural habitat conditions might have on species telomere dynamics. A follow-up study conducted on the same colonies emphasises that telomere length varies in complex ways with spatial habitat use, foraging efficiency, sex and prey selection (Young et al. 2015). Recently, a study on telomere dynamics of six different pied flycatchers *Ficedula hypoleuca* populations across Europe indicates between-population variation in telomere length, which seems linked to early life conditions (Kärkkäinen et al. 2021).

The influence of habitat heterogeneity on birds' telomere length has also been demonstrated at a more localised scale. For instance, American redstarts *Setophaga ruticilla* wintering in a low-quality habitat showed shorter telomeres and faster shortening rate the following year than birds in an adjacent high-quality habitat (Angelier et al. 2013). Likewise, in pied flycatchers, females nesting at sites with constant predation risk, due to the presence of pygmy owls *Glaucidium passerinum*, showed faster telomere shortening, compared to control sites (Kärkkäinen et al. 2019). Moreover, the study of telomere dynamics across the lifetime of multiple cohorts in the insectivorous Seychelles warbler *Acrocephalus sechellensis* not only indicated a marked spatio-temporal effect (Bebbington et al. 2017) but also found evidence that harsher environmental conditions (i.e. lower insect abundance) are negatively related with telomere length (Spurgin et al. 2018). Finally, one study on the effects of elevation on telomeres of great and coal tit nestlings (*Parus major* and *Periparus ater*, respectively) consistently found faster telomere shortening in birds from high altitude, where environmental conditions are cooler and the nutritional conditions are potentially limited (Stier et al. 2016).

Several studies on the physiological impacts of urbanisation on wild birds have compared telomere lengths from populations exposed to different degrees of human presence. Urban areas have been shown to negatively impact telomere length in blackbirds *Turdus merula* across five European cities, i.e. shorter telomere lengths in urban compared to rural birds (Ibáñez-Álamo et al. 2018). The negative effect of urbanisation on telomere length was demonstrated, via the reciprocal cross-fostering of urban and rural great tit nestlings, suggesting that the effect is not the result of genetic or early maternal effects but of the urban environmental conditions experienced during development (Salmón et al. 2016). In contrast, in another study in great tits, telomere length of 14-days old chicks did not differ between rural and urban populations located in two different geographical areas of France (Biard et al. 2017). European great tit nestlings living closer to roads also had shorter telomeres (Grunst et al. 2020), as observed in the tree swallow in North America (*Tachycineta bicolor*; Injaian et al. 2019). Finally, in a metal-contaminated habitat, great tit nestlings (but not adults) had shorter telomeres than control individuals, whereas, in pied flycatchers inhabiting the same locations, telomere length was unaffected by contamination, suggesting developmental and species-dependent responses to contaminants (Stauffer et al. 2017).

The amount of information on telomeres in a spatial context is more limited for other endotherms. One study on American black bears *Ursus americanus* addressed, from a biogeographic approach, the variation in telomere length across Colorado State metapopulations of this species (Kirby et al. 2017). This study indicates that individual characteristics such as age, sex or genetic relatedness do not correlate with telomere length. In contrast, environmental variation across the broad-scale latitudinal pattern explained the observed differences in telomere length, i.e. shorter telomeres in bears from higher latitudes. This relationship may arise from the combination of multiple abiotic factors that differ along the studied latitudinal gradient, such as cooler temperatures or increased precipitation at high latitudes, which ultimately influences habitat quality (Kirby et al. 2017). Moreover, the lack of genetic differences supports the idea that genetic isolation is not the driving force behind the observed differences in bear telomere length. At a narrower scale, old-age European roe deer *Capreolus capreolus* inhabiting a low-productivity forest with poor-quality soils and summer droughts have shorter telomeres compared with individuals from a fertile soil and high-productivity forest (Wilbourn et al. 2017). Importantly, as for birds, some studies on mammal populations have focused on the role of anthropogenic disturbances or pollution. For example, populations along a coal gradient pollution in Brazil of collared tuco-tuco *Ctenomys torquatus*, an herbivorous and subterranean rodent, showed an inverse correlation between telomere length and coal exposure, i.e. shorter telomeres in populations from more polluted environments (Matzenbacher et al.

2019). Similarly, bank voles *Myodes glareolus* inhabiting the Chernobyl Exclusion Zone showed shorter telomeres and higher telomerase expression, in some tissues, than in control areas (Kesäniemi et al. 2019).

In general terms, the available studies in endotherms demonstrate telomere length or telomere shortening differences across populations, and often these can be linked to less benign environmental conditions. However, only a handful of studies have tried to empirically address the link between environmental factors and telomere length dynamics across populations; thus, based on the available information, it is still difficult to interpret the relative contribution of particular environmental conditions to the observed variation in telomere length.

Studies on ectotherms

So far, few studies have compared telomere length or its dynamics among populations of ectothermic vertebrates (Olsson et al. 2018). These studies have mostly covered a relatively small spatial scale, and in contrast to the research conducted on endotherms, only one study has assessed the impact of urbanisation on ectotherm telomeres. Molbert et al. (2021) compared telomere length of European chub *Squalius cephalus* from urban and agricultural rivers and found a negative effect of urbanisation on telomere length. In a different study, juvenile brown trout *Salmo trutta* telomere length from 10 natural Estonian populations negatively correlates with past river water temperature and individual body size (Debes et al. 2016), which suggests a role of past thermal stress on telomere attrition. McLennan et al. (2016) found faster telomere shortening in Atlantic salmon *Salmo salar* growing at higher rates, a relationship that was only present under harsh stream conditions, i.e. high-altitude streams with colder temperature and greater predator density. Likewise, telomere lengths of common lizards *Zootoca vivipara* have been shown to negatively correlate with population extinction risk within the species' Southern distribution in France (Dupoué et al. 2017). This latter study exemplifies the promising use of telomeres as a biomarker for an advanced assessment of health and viability of wildlife populations. In the Algerian sand lizard *Psammodromus algirus*, populations along an altitudinal gradient of 2200 m showed differences in telomere length, although this variation did not follow a linear pattern and seems to be linked to among-population differences in age structure (Burraco et al. 2020b). Following a similar ecological set-up, Fitzpatrick et al. (2019) found that warm and cool highland populations of spotted snow skinks *Niveoscincus ocellatus* had similar telomere lengths, but surprisingly, telomeres lengthened in individuals exposed to hot basking conditions regardless of their climatic origin. In loggerhead turtles *Caretta caretta*, oceanic- and neritic-foraging first-time nesters did not show differences in telomere length despite their clear differences in feeding habitat (Hatase et al. 2010). In an amphibian, the common frog *Rana temporaria*, inhabiting ponds within a Swedish island system, populations from temporary ponds (i.e. high seasonal pond desiccation risk), showed shorter telomeres than populations under lower desiccation risk (Burraco et al. 2017). In another amphibian, the natterjack toad *Epidalea calamita*, a study across a continental case of dwarfism in Southern Spain found telomere differences between populations, but these did not match population variation in body size or habitat type and occurred in the absence of genetic isolation (Hyeun-Ji et al. 2020). Finally, a one-year longitudinal common-garden experiment investigated whether telomere dynamics, in the Sardinian tree frog *Hyla sarda*, differ in populations with contrasting biogeographic history (Canestrelli et al. 2021). At the beginning of the study, telomere length was similar between populations. However, while telomere length did not vary over one year within historically stable populations, a remarkable telomere elongation was observed in those populations from a recent range expansion.

It is important to highlight that within invertebrates, the study of telomeres is limited, and therefore the information available across spatial patterns is also limited. To the best of our knowledge, only three studies have compared telomere lengths between invertebrate populations (Table 1). Gruber et al. (2014) measured telomeres in two contrasting mollusc populations regarding age in the Iceland cyprine *Arctica islandica*, the longest-lived non-colonial animal. They found that telomere length of the short-lived population, with a maximum lifespan of 40 years, did not differ from a long-lived population, with a maximum lifespan of 226 years. In this cross-sectional study, telomere length was measured over a wide age range, and importantly, other processes such as selective mortality of short telomere individuals or local adaptation might have obscured any differences. Another study compared Atlantic and Mediterranean populations of the fissiparous starfish *Coscinasterias tenuispina* and found Mediterranean populations had longer telomeres and smaller body size than the Atlantic ones (Garcia-Cisneros et al. 2015). Finally, telomere length did not vary among populations of the common sea urchin *Paracentrotus lividus* exposed to contrasting levels of trace elements; however, the relationship between body size and telomere was significantly negative only in the populations exposed to trace elements (Coupé et al. 2019).

Contrary to endotherms, studies on ectotherms (both vertebrates and invertebrates) showed a higher disparity in terms of telomere differences linked to environmental variation: 6 out of 13 studies did not find consistent differences between populations or habitats. However, the small number of studies in combination with the taxonomic differences, from sea urchins to squamates, means that it is a challenge to obtain an accurate general picture at this point. Therefore, further studies are needed to disentangle the relationship between environmental conditions, life-history traits (such as growth or development) and telomere dynamics in ectothermic animals.

Overall, the information on telomere length across spatial scales is strongly biased towards endotherms and in particular birds (comprise more than half of the studies in Table 1), which to a certain extent mimics the general pattern observed in the telomere literature (Olsson et al. 2018). Importantly,

we still lack understanding of the role of natural environmental conditions as drivers of telomere variation within a species, as the available studies usually include a limited number of populations or sites. Further efforts to increase spatial replication to cover the environmental variation present across species distribution will help to identify the abiotic and biotic conditions shaping species telomere dynamics. This information may help to improve our understanding of the physiology underlying ageing patterns and to predict mortality in the wild (Kaszubowska 2008, Epel et al. 2009, Barrett et al. 2013, Giraudeau et al. 2019). Finally, most of the available studies are cross-sectional, meaning that telomeres were measured once in an individual's lifetime. Cross-sectional comparisons raise issues for understanding the impact of environmental changes across populations, as differences in age structure and the possible selective disappearance of individuals can introduce biases in the interpretation of a given telomere length. A longitudinal sampling design will therefore provide critical information on the relationship between telomere length and individual performance, potentially advancing the understanding of populations' resilience under future environmental change scenarios.

Using telomere length information to develop mechanistic species distribution models: an empirical case study

Health and fitness assessments often allow to identify when a population is at risk of decline (Ceballos et al. 2017, Kophamel et al. 2021). Telomere dynamics are commonly used as a surrogate of individual health and lifespan; however, their potential application for estimating species distribution and resilience has not been empirically tested. Here, as a first approach, we used information contained in Dupoué et al. (2017) to explore the relevance of combining telomere information with environmental predictors to obtain spatial inferences on species habitat suitability. Dupoué et al (2017) estimated telomere length using telomere restriction fragment (TRF) analysis, the gold standard for telomere length measurement, in 10 populations of the common lizard *Zootoca vivipara* in southern France (10 yearlings per population, n = 100 individuals; Fig. 2). In this species, juvenile telomere length has previously been shown to explain mortality risk (Dupoué et al. 2020). Using this telomere information, we aimed to 1) corroborate the association between telomere length and local environmental variables; 2) explore the relationship between a SDM built from telomere length estimates and one SDM built from species presence/pseudo-absence data; 3) check for the power of spatially modelled telomere length estimates to predict habitat suitability.

We initially assessed the association between telomere length and environmental variables at the local scale (latitude 43–46°N, longitude 2–5°E) using bioclimatic data contained in the CHELSA database (Karger et al. 2017, Supporting information). After model selection, two uncorrelated environmental variables remained in the final model: $Bio6_S$ (minimum temperature of the coldest month) and $Bio7_S$ (temperature annual range) (see the Supporting information for details). Telomere length was negatively associated with $Bio6_S$ and its quadratic effect *Bio6QS* (both p-values < 0.001; Supporting information), whereas an association with linear and quadratic effects of $Bio7_S$ was not detectable (Supporting information). The resultant model showed an R^2 of 0.73. We then used the fitted model estimates to predict the species telomere length within the studied area (Fig. 2a; Supporting information).

We further calculated a correlative habitat suitability model for *Zootoca vivipara* using data from local occurrences archived in the Global Biodiversity Information Facility (GBIF) and bioclimatic variables from the CHELSA database (Karger et al. 2017, Supporting information). The correlative habitat model (TSS = 0.82, sensitivity = 0.91 and specificity = 0.91) indicated that *Bio2* (i.e. mean diurnal temperature) and *Bio5* (i.e. maximum temperature of the warmest month) were the main environmental variables explaining the occurrence of the species in the study area (variable importance 0.10 and 0.96 respectively; Supporting information). The presence of *Zootoca vivipara* was negatively associated with the variable *Bio5* whereas *Bio2* did not affect its distribution (Supporting information). We used the results from this habitat suitability model to compare them with the previously calculated spatial distribution of telomere length estimates. We found a strong positive correlation between predicted values obtained from both models, i.e. telomere length estimates and habitat suitability (p-value < 0.001, $R^2 = 0.56$; Fig. 2b, Supporting information).

As a complementary analysis, we explored the use of telomere length information to predict the distribution of common lizards in the study area. We used the 10th percentile of the telomere lengths estimated by Dupoué et al. (2017) to establish a telomere length threshold of 11.89 kilobases (kb). We defined this cut-off length as a hypothetically short telomere length that might limit the viability of populations of this lizard species. Using this value, we converted the spatial telomere length estimates to presence (> 11.89 kb) or absence (< 11.89 kb) and validated these results with presence/pseudoabsence data obtained from GBIF. The validation of these binary telomere length predictions showed a high sensitivity of 0.85, specificity of 0.76 and accuracy of 0.81.

Overall, this exploratory modelling approach suggests that telomere length can be driven by environmental variables and that it is positively associated with correlative habitat models. Moreover, in our study, the modelled telomere length estimates allow to infer species distribution. This latter result exemplifies the possible relevance of including telomere length measurements in future mechanistic SDMs. Correlative habitat models approach relates species observations to spatial data and uses simple observations of presence/absence of the species. Nonetheless, this has its limitations as they are not able to capture the mechanistic niche of the species (Guisan et al. 2017). Instead, mechanistic models, based on measures of fitness-related traits, can describe the fundamental niche (Kearney and Porter

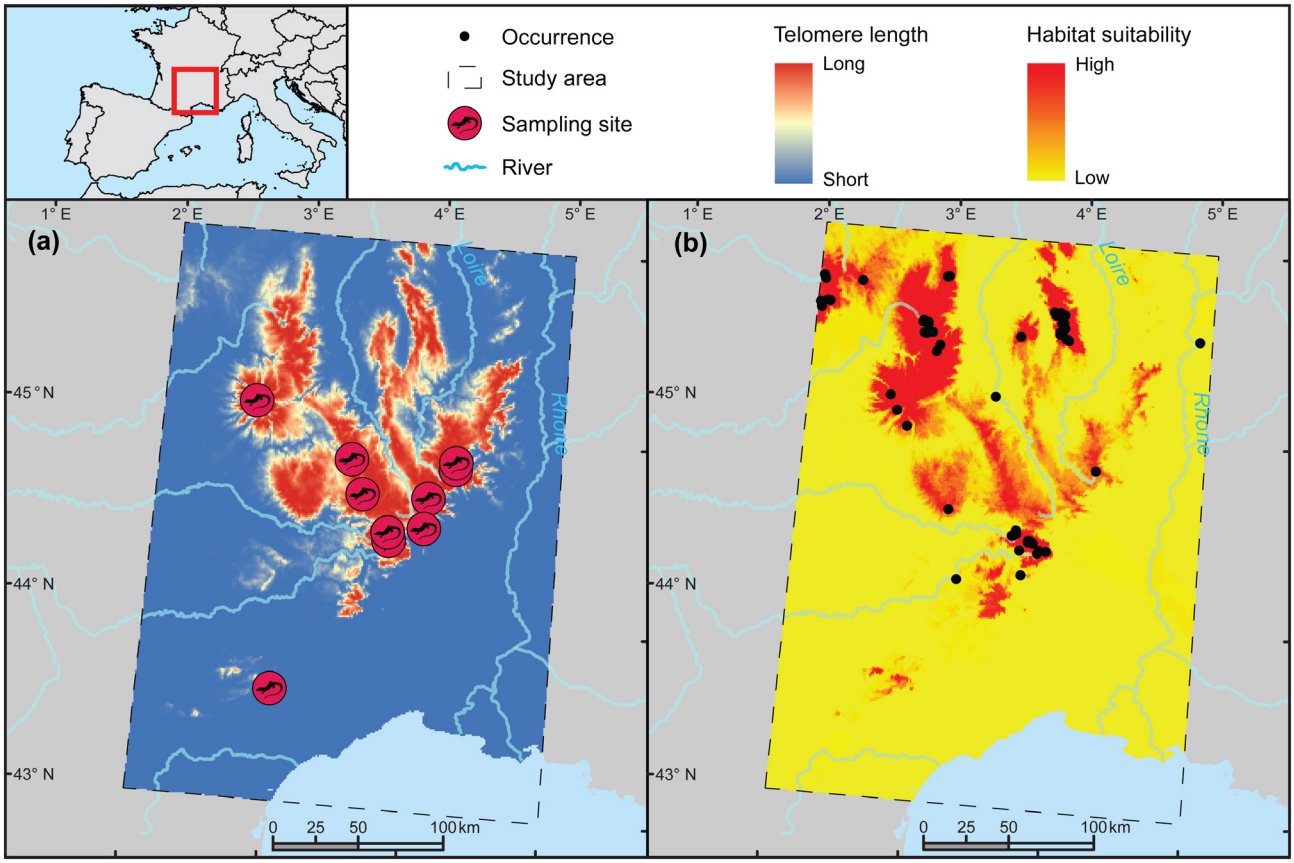

Figure 2. (a) Spatial distribution of predicted telomere lengths for common lizard *Zootoca vivipara* in the study area located in southern France (upper map). The analysis is based on the telomere measurements from Dupoué et al. (2017) combined with the bioclimatic variables obtained from the CHELSA database (see main text and Supporting information). Symbols represent the 10 populations sampled in Dupoué et al. (2017). (b) Habitat suitability predictions for common lizard obtained from models using presence (black circles) and pseudo-absence data downloaded from the Global Biodiversity Infrastructure Facility (GBIF) and combined with the bioclimatic variables obtained from the CHELSA database (see main text and Supporting information). In both maps, predictions are based on 1 × 1 km pixels.

2009) which may allow to improve predictions e.g. under future climate change scenarios (Lyons and Kozak 2020). Despite the limitations in our example (e.g. limited spatial and temporal replication), we encourage future research in this direction by, for example, implementing Bayesian hierarchical models to reduce the uncertainty in the estimates (Talluto et al. 2016) or using threshold models that can allow to better understand the relation between telomere length and environmental variables (Berman et al. 2009, Donohue et al. 2015).

Measuring telomeres across spatial patterns – theoretical and practical considerations

Telomere length, at a given developmental point or age, is the result of the genetic background plus the environmental effects that individuals experience from conception. Understanding telomere dynamics in wild populations across spatial patterns may help to improve our current knowledge on habitat suitability and species distribution. Nonetheless, there are some key practical and theoretical considerations that future studies, combining biogeographic and telomere information, may pay attention beforehand:

First, for a given species, whether telomere length and/or its dynamics can be considered as a reliable marker of health or lifespan. The existence of links between fitness-related traits (e.g. survival or lifetime reproductive success) and telomere information is essential to interpret differences in telomere length observed either in the field or in common-garden experiments. Lack of existing knowledge might limit the use of telomere information in mechanistic SDMs. Also, the knowledge of a species telomere structure and the mechanisms underlying maintenance are important from a technical perspective (Nussey et al. 2014). In some species, interstitial telomeric sequences are present in the interior of chromosomes, but only terminal sequences shorten with age (Foote et al. 2013). If the among-individual variation in interstitial sequences is high, and they are not taken into consideration, it can

lead to misinterpretations of the telomere dynamics. Furthermore, some species present ultralong telomeres that provide information on developmental history but not on their ageing pattern, hence the use of techniques that yield a single estimate of telomere length (e.g. qPCR or dotblot) might obscure any interpretation (Atema et al. 2019). Also, it is well known that certain species present chromosomic polymorphisms, i.e. variable number of chromosomes between and within populations (Fredga and Bergström 1970), and this aspect might need to be accounted for.

Second, to carefully consider the spatial scale and pattern of interest. For example, considering past and current abiotic and biotic conditions of the study sites, together with the corresponding phylogeographic components, will improve the interpretation of telomere dynamics. Furthermore, these studies will benefit from an adequate spatial replication, e.g. sampling across a well-defined spatial gradient covering a representative portion of the species or clade distribution. In addition, temporal replication would allow to control for possible cohort and cross-generational effects. Overall, these measures should help to quantify spatial autocorrelation, to control for spatial and temporal independence, and to increase the statistical power of any biogeographical approach (Becker et al. 2020).

Third, understanding the species biology is essential to accurately design the sampling procedure, i.e. time-lapse between samples or life stages, and to identify the target tissue to measure telomere length (preferably a minimally invasive one). This can be particularly relevant for organisms inhabiting several environments across their lifetime, e.g. amphibians or odonates. Therefore, longitudinal samples would be ideally collected from the same individual or family in each environment. Individuals of migratory species, and of species with complex life cycles, often face contrasting conditions across their life, and telomere length should be estimated in each of those environments.

Fourth, to obtain experimental information on the abiotic and biotic factors influencing telomere dynamics and its performance outcome in the selected study system. Most studies on telomeres in ecology and evolution are based on correlational data. While they provide a promising starting point, we need further experimental data on telomere length responsiveness to key environmental conditions. Although this might be challenging for certain taxa, it also has the strength of providing direct 'cause-effect' information, which is an important aspect when applying certain approaches for SDMs (Talluto et al. 2016).

Fifth, to control for individual factors. As previously mentioned in this review, telomere length seems to have an important heritable component; thus, studies comparing multiple populations need to be aware of the importance of disentangling environmental from genetic effects sensu lato. This might be a difficult aspect in natural populations, but conducting common garden or translocation experiments, together with the study of environmental variation, could be a useful approach (Salmón et al. 2016, Fitzpatrick et al. 2019, Canestrelli et al. 2021). The use of experiments may also help to understand whether acclimation or local adaptation is governing the telomere dynamics, although this is a virtually unexplored aspect yet. Also, the collection of longitudinal samples provides critical information for telomere dynamics, for example ruling out within-individual changes in telomere length from the selective disappearance of individuals with shorter/longer telomeres (Salomons et al. 2009, McLennan et al. 2017, Salmón et al. 2017). Notably, in natural populations, a longitudinal design will also provide an opportunity to directly investigate the effect of natural environmental variation over time (Spurgin et al. 2018). However, cross-sectional sampling designs can also be informative, for example, in small-bodied species or to collect at specific age tissues that require terminal sampling, especially if it is possible to conduct experiments with no differential mortality between populations or treatments.

These considerations may provide an initial guideline and assist in improving the design of future studies implementing the use of telomere length and its dynamics in biogeographic research. We acknowledge that the combination of spatial and telomere data is not straightforward and may be limited by the underlying characteristics of the study system, making it difficult to collect age-specific estimates. Moreover, simultaneously addressing some of the above-mentioned points might be challenging in the same system. The combination of field and laboratory studies in different taxa will help us to achieve a better understanding of the role of past, current or future environmental conditions on telomeres and ultimately help to improve the knowledge of physiological ageing patterns across spatial scales.

Conclusions

This review demonstrates the existence of divergence in telomere length and/or its dynamics across populations inhabiting contrasting environments, and suggests that telomeres might be a useful marker to understand between-population variation in ageing patterns. However, current telomere information on wild telomeres (mainly based on avian and mammalian studies) denotes that the relationship between fitness-related components and telomere length is variable among species; thus, the validation of telomere information as a health or fitness biomarker is an important pre-requisite when using telomere information in biogeographical approaches. Even though further work is needed, the use of telomere estimates in a spatial context, including its implementation in SDMs, could deepen our understanding of differences in ageing patterns across populations and advance our knowledge about the resilience of telomeres under environmental change. For instance, telomere data may lead to a more complete understanding of the consequences of metabolic increases caused by global change (Dillon et al. 2010, Seebacher et al. 2015) and therefore improve our knowledge of current biodiversity losses, although there is a long road ahead to meet this aim.

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Author contributions

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Data availability statement

Telomere data analysed in this study comes from Dupoué et al. (2017). The R code used for the spatial and telomere analyses is available from the Dryad Digital Repository (<https://doi.org/10.5061/dryad.fqz612jtc>).

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